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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,345	02/26/2007	Nobuaki Takahashi	081356-0262	3671

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	
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08/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/584,345	**Applicant(s)** TAKAHASHI ET AL.	
	Examiner Phillip Gambel	**Art Unit** 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 August 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *13 August 2010*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *137-139*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Phillip Gambel/
Primary Examiner, Art Unit 1644

Continuation of 3. NOTE: evidence filed after a final action but on the date of filing a Notice of Appeal is not entered because applicant failed to provide a showing of good and sufficient reasons why the evidence was not earlier presented. also, note that the methods and results of the experiment where the 4D11G4PE antibody was administered at a concentration of 100 mg/kg does NOT have a corresponding declaration by a person in position to corroborate the fact. .

Continuation of 11. does NOT place the application in condition for allowance because: essentially for the reasons of record. Applicant's arguments and the examiner's rebuttal are essentially the same of record. See the previous Office Action, mailed 03/30/2010, for a more complete analysis.

In contrast to applicant's / Takahashi's assertions (of record), the teachings of the primary and secondary references are consistent with the applicant's Takahashi's assertions with respect to modifying antibodies, including the claimed anti-CD40 antibodies to decrease the immunogenicity and the binding to Fc receptors for the same reasons as applicant's/Takahashi's assertions.

For example, see the following excerpt in paragraph [0011] on page 4 and paragraph [0045] on page 12 of the evidentiary reference EP 1391464.

Specifically, there may be a risk that the antibodies would become agonistic antibodies. Even if the antigenicity is low, anti-CD40 antibodies may be cross-linked with antibody receptors (FcR). From these points, a preferred antagonistic antibody is a human antibody, which binds specifically to CD40, suppresses the binding of CD40L, and does not activate CD40 even by cross-linking, and exhibits weak binding to FcR.

While applicant asserts that nothing in the cited art even hints at the possibility that a mutation acknowledged to reduce effector function also could abolish residual agonistic activity, common to antagonistic anti-CD40 antibodies,

again, the secondary references are all consistent with modifying IgG4 subclass with the same S228P and L235E (PE mutation) for the very same reason as the primary references as well as applicant's/Takahashi's assertions.

Consistent with applicant's remarks that according to the application,"agonistic activity" refers to an action enhancing binding of a ligand to CD40 expressed on the surface of such cells as B cells, tumor cells or dendritic celsl, or an action of providing the CD40-expressing cells with at least one effect which the CD40 ligand makes on the CD40-expressing cells (e.g., see page 39, lines 11-15 of the specification);

the prior art providing for making the same modificaitons to a known antibody, wherein the antagonistic anti-CD40 antibody would have been expected to maintain its antagonistic properties and would have been expected to decrease and minimize it undesirable agonistic properties by diminishing Fc-mediated functions / properties consistent with the definition of the specification.

The prior art provides, not only a finite number of identified, predictable solutions to modifying antibodies, but provides for the very same modifications of therapeutic antibodies to the IgG4 subclass with the S228P and L235E mutations in order to decrease immunoglobulin effector function and, in turn, cross-linking.

As to whether there is a dispute to the unexpectedness of applicant,

applicant does not appear to dispute the basic premise of the prior art teachings of modifying therapeutic antibodies of interest to IgG4 antibodies with the very same mutations claimed in order to diminish or abolish immunoglobulin effector functions.

Whether the results presented in the Interview held on 07/28/2010 or presented herein are unexpected, the level of residual agonistic properties may be more of degree rather than kind, as the prior art clearly taught the ordinary artisan to modify therapeutic antibodies with the same or nearly the same properties of diminishing or abolishing immunoglobulin effector function such as binding to Fc receptors and its corresponding cross-linking, which, in turn, is consistent with the claimed invention and the reasons behind the claimed invention.

While applicant's relies upon the modulation of clenoliximab in vivo as described by Reddy et al. (J. Immunol. 164: 1925-1933, 2000) (1449; #F8) and Newman et al. (Clin. Immunol. 98: 164-174, 2001) (1449; #F14) to indicate cross-linking in vivo or at least at higher doses in vivo (versus in vitro);

Newman et al. notes that the mechanism for modulatin is unknown (e.g., see page 173, column 1, paragraph 1).

Further, it is noted that both Reddy et al. and Newman et al. stand for the entry of clenoliximab (with the same antibody IgG4 / mutations modifications as taught by the prior art and claimed) into clinical trials for treatment.

The IgG4 PE modifications taught by the prior art are consistent with the very same advantages of the goals the PE modifications as well as the possible disadvantages not making such modifications as the claimed invention.

Applicant's arguments have not been found persuasive.

Also, note that applicant's arguments rely, at least in part, upon evidence filed after a final action but on the date of filing a Notice of Appeal, which is not entered because applicant failed to provide a showing of good and sufficient reasons why the evidence was not earlier presented. Also, note that the methods and results of the experiment where the 4D11G4PE antibody was administered at a concentration of 100 mg/kg does NOT have a corresponding declaration by a person in position to corroborate the fact. . .